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(54) **Title:** CERAMIDE DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

(57) **Abstract:** The present invention relates to the use of: (i) a ceramide, a ceramide analogue, a phytoceramide; or (ii) a compound which is metabolisable into or otherwise capable of releasing a ceramide, a ceramide analogue or a phytoceramide; or (iii) a compound which modulates the level of endogenous ceramide as a pharmaceutically active agent in the production of a medicament for the treatment of an inflammatory disorder. The invention also relates to a method of inhibiting monocyte recruitment, and/or adhesion and/or transmigration to sites of inflammation and/or of inducing growth arrest in proliferating monocytes, comprising exposing the monocytes to a therapeutically effective amount of a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolised into or breaks down to release a ceramide, a ceramide analogue, a phytoceramide in situ, or a compound which modulates the level of ceramide as a pharmaceutically active agent.

isolated from the whole blood of patients with RA possess elevated adherence to fibronectin and resting or activated endothelial cells. The appearance of monocytes within the synovium of rheumatoid patients is followed by their differentiation into tissue macrophages and type A synoviocytes, which contribute to joint destruction through secretion of matrix metalloproteinases.

In the past, many successful anti-inflammatory drugs have been discovered fortuitously: these include non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit prostoglandins, disease modifying anti-rheumatic drugs and cytotoxic agents which inhibit cellular replication. None of these classes of anti-inflammatory drugs is specifically targeted to inflammatory cells and therefore may result in undesirable side effects. More recently work has been focussed on growth factors, such as Tumour Necrosis Factor (TNF) which is a potent inflammatory cytokine, and its neutralisation or blocking using antibodies. This treatment can lead to severe side effects and also can be prohibitively expensive.

It is an object of the present invention to provide an alternative medicament for the treatment of inflammatory disorders which obviates or mitigates one or more of the above disadvantages.

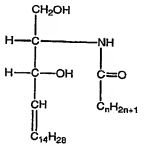
According to a first aspect, the present invention resides in the use of:
(i) a ceramide, a ceramide analogue, a phytoceramide; or
(ii) a compound which is metabolisable into or otherwise capable of releasing a ceramide, a ceramide analogue or a phytoceramide; or
(iii) a compound which modulates the level of endogenous ceramide,

as a pharmaceutically active agent in the production of a medicament for the treatment of an inflammatory disorder.

The invention resides in the surprising discoveries that ceramides, ceramide analogues and phytoceramides inhibit monocyte recruitment, adhesion, proliferation and transmigration to sites of inflammation.

Lipids, which include ceramides, represent a useful class of pharmaceutical compounds as they can evade the immune system due to their flexible structures and their ability to rapidly partition into membranes.

Ceramide comprises a sphingosine molecule linked to a second fatty acid by an amide bond (formula 1).



Formula 1

Preferably, said ceramide, ceramide analogue or phytoceramide has the structure of formula 1 where n is no more than 18, preferably no more than 8, and more preferably from 2 to 6.

Preferably, said compound which modulates the level of endogenous ceramide is one which increases levels of endogenous ceramide or

reduces the degradation of endogenous ceramide. For example said compound may be an inhibitor of ceramidase, which normally acts to degrade ceramide, such as DMAPP which blocks alkaline ceramidase, or B13 which blocks acid ceramidase.

According to a second aspect of the present invention there is provided a method of inhibiting monocyte recruitment, and/or adhesion and/or transmigration to sites of inflammation and/or of inducing growth arrest in proliferating monocytes, comprising exposing said monocytes to a therapeutically effective amount of a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolised into or breaks down to release a ceramide, a ceramide analogue, a phytoceramide in situ, or a compound which modulates the level of ceramide as a pharmaceutically active agent.

According to a third aspect of the present invention there is provided a method of treating a patient having an inflammatory disorder comprising, administering to said patient as a pharmaceutically active agent a therapeutically effective amount of a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolised into or breaks down to release a ceramide, a ceramide analogue, a phytoceramide in situ, or a compound which modulates the level of endogenous ceramide.

Preferably said treatment reduces recruitment, adhesion and/or transmigration of monocytes to sites of inflammation and/or induces growth arrest in proliferating monocytes.

Preferably, said medicament according to the first aspect is characterised in that it acts by inhibiting at least one of and preferably all of monocyte recruitment, adhesion, transmigration to an inflammatory site and growth of proliferating monocytes.

Preferably, said medicament comprises means for delivery of the pharmaceutically active agent to an inflammatory site.

Preferably, said delivery means allows selective delivery to the inflammatory sites.

Said delivery means may be any known delivery means e.g. a surfactant-based vesicle delivery system, for example liposomes, a viral vector delivery system, an antibody associated delivery system or any other ligand-receptor associated targeted delivery system.

Administration of said medicament may be by any convenient route e.g. by intravenous, intramuscular, or subcutaneous injection, topical administration as an ointment, salve, cream or tincture, oral administration as a tablet, capsule, suspension or liquid and nasally as a spray (e.g. aerosol).

In the methods or medicament of the present invention, said pharmaceutically active agent may be in admixture with one or more excipients, carriers, pH regulators, flavourings, colourings, preservatives, or other commonly used additives in the field of pharmaceuticals as appropriate for the mode of administration.

Examples of inflammatory disorders which may be suitable for treatment by the medicament according to the first aspect include, rheumatoid arthritis, atherosclerosis, acute or chronic inflammatory lung disease and inflammatory bowel disease.

Preferably, particularly when said pharmaceutically active agent is administered systemically, it is administered at a level to obtain a steady state blood concentration of ceramide, ceramide analogue, or phytoceramide of 1 to 20mg/l, more preferably 2 to 10mg/l, most preferably 3 to 8mg/l.

Preferably, when said pharmaceutically active agent is delivered non-systemically sufficient agent is delivered to achieve a concentration of ceramide, ceramide analogue, or phytoceramide in the inflammatory cells of greater than 100 amol, more preferably from 500 amol to 5 fmol, most preferably from 750 amol to 3 fmol.

When said pharmaceutically active agent is a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolisable into or otherwise capable of releasing a ceramide, a ceramide analogue or a phytoceramide, said blood and cellular concentrations may be achieved by administering a dosage of pharmaceutically active agent of 10 to 100 mg/day, or preferably, 20 to 80 mg/day.

Embodiments of the invention will now be described by way of example only, with reference to the accompanying drawings in which:

Fig. 1 is a graph showing the effect of ceramide on *in vitro* monocyte recruitment to LPS activated endothelial cells,

Fig. 2 is a graph showing the effect of exposure to ceramide for 16 hours on the membrane expression of a number of cell surface adhesion molecules.

Fig. 3 is a graph showing the effects of exposure to ceramide on the numbers of monocytes becoming growth arrested.

Materials and Methods

Ceramide stock solution production

C_2-ceramide (N-acetyl-sphingosine) and C_6-ceramide (N-hexanoyl-sphingosine) (obtained from Biomol Research Laboratories, Plymouth Meeting, PA, USA) were separately dissolved in anhydrous DMSO to a stock solution of 20mM. Subsequent dilutions were made in 1mM fatty acid free BSA.

Cell growth conditions

The acute human monocytic cell line, U937 was maintained in RPMI 1640 media, supplemented with 10% heat inactivated foetal calf serum and 1% penicillin/streptomycin. Cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 and 95% air.

Determination of cell numbers

The number of viable cells per ml was determined by trypan blue exclusion using an improved Neubauer haemocytometer (Weber Scientific International Ltd., Teddington, UK).

Treatment of cells with ceramide solutions

Cells at a concentration of $2x10^6$/ml were serum starved for 4 hours prior to treatment with ceramide. Cells were treated with C_2- or C_6-ceramide for the times and at the concentrations noted in the figures. Incubations were performed at 37°C in a humidified 5% CO_2/95% air incubator.

Cell adhesion assay

The cell adhesion assay was performed as described by Woollard (Woollard KJ, Phillips DC, Griffiths HR. Direct modulatory effect of CRP on primary human monocyte adhesion to human endothelial cells. Clin. Exp. Immunol. 2002; 130, 256-262.). Human Umbilical Vein Endothelial Cells (HUVEC) were obtained from umbilical cords by digestion with collagenase and cultured in Endothelial Growth Medium (EGM; BioWhittaker) at 37°C, 5% CO_2, 95% air humidity, as described previously (Jaffe EA, Nachman RL, Becker GC *et al.* Culture of human endothelial cells derived from umbilical veins. J. Clin. Invest. 1973; **52**: 2745-2756. Holland JA, Pritchard KA, Rogers NJ *et al.* Perturbation of cultured human endothelial cells by atherogenic levels of LDL. Am. J. Pathol. 1988; **132**: 474-478.). HUVEC were grown to confluence in 24 well plates (Orange Scientific) up to passage 3 in EGM media and were

used 24 hours after confluence. HUVEC were washed and LPS (1μg/ml) or HBSS as control added for 0, 5 or 24 hours (37°C, 5% CO_2, 95% air humidity). Each well was then washed twice with 1ml of M199 (Sigma), before addition of monocytes. Monocytes were resuspended to $5x10^6$/ml and labelled with 2', 7'-bis-2-carboxyethyl-5-(6)-carboxyfluorescein-acetoxymethylester (BCECF-AM; Sigma; 10μg/ml) for 30 minutes at RT in the dark. Dye loading was quenched by adding 10mls of PBS (0.1% BSA) and centrifuging at 235g for 8 minutes. Monocytes were washed and resuspended in M199. Monocytes ($0.5x10^6$/ml) were added to HUVEC and incubated for 30 minutes, under the above described culture conditions. Non-adhered cells were removed by centrifugation of inverted plates (Weber C, Wolfgang E, Weber K *et al*. Increased adhesiveness of isolated monocytes to endothelium is prevented by vitamin C intake in smokers. Circulation 1996; **93**: 1488-1492.). Lysis buffer (1ml; 0.1% Triton-X; Sigma) was added to each well and incubated in the dark at RT for 30 minutes. Lysed cells were pipetted into 96 well plates (Nalge Nunc (Europe) Ltd, Hereford, UK) in replicates of 9 and fluorescence was measured at an excitation of 485 nm and emission of 535 nm on a Wallace Spectrofluorimeter.

Flow cytometry

Monocytes were incubated with 0-20μM C_2- or C_6- ceramide in serum free medium for 16 hours and then washed three times in PBS. Subsequently samples were analysed for CD11b, CD31, CD18, CD11a and CD62L expression by flow cytometry (Beckman Coulter, Miami, Florida, USA), using appropriate three-way colour compensation and isotype negative controls for each sample. Following treatment, cell samples (monocytes)

were incubated with appropriate primary (anti-human) Mab (CD11b-RPE [ICRF44]), CD31-RPE [WM59], CD11a-FITC [AT10], CD62L-RPE-Cy5 [TUK-4]; Serotec Ltd, Kidlington, UK; 10µl/10^6 cells or 100µl PWB) on ice in the dark for 30 minutes. Optilyse (Beckman Coulter) was added to lyse RBC and fix the samples. Samples were vortexed and incubated in the dark at RT for 10 minutes. Each sample was diluted 1:2 with Isoton (Beckman Coulter), vortexed and left at RT in the dark for no longer than 4 hours, until analysis by flow cytometry.

Examples

Example 1, Effect of ceramide on the recruitment of monocytes to the endothelium.

Figures 1 A, B and C show the effect of ceramide on U937 monocyte recruitment to confluent HUVEC endothelial monolayers which have been activated with lipopolysaccharide (LPS) for varying times. LPS is a bacterial antigen which stimulates the immune response. It is used as a model of inflammation and activates integrins and adhesion molecules on endothelial cells and monocytes. After LPS treatment, the HUVEC cells were exposed for 30 min to monocytes which had previously been incubated in media containing ceramide for 16 hours. Figure 1A is a negative control (no LPS), Figure 1B 5 hours exposure to media containing 1µg/ml LPS, Figure 1C 24 hours exposure to media containing 1µg/ml LPS. In all figures, column 1 is a negative control (no ceramide), column 2 20µM C_2-ceramide, column 3 20µM C_6-ceramide, column 4 10µM C_6-ceramide.

Figure 1A shows that ceramide has no significant effect on the level of monocyte recruitment to non LPS activated HUVEC monolayers.

Figure 1B shows that after 5 hours exposure to LPS, cells then exposed to 20μM C_2- or C_6-ceramide show a significant reduction in the recruitment of monocytes to about 50% of the control level of recruitment. There is less reduction in recruitment when the cells are exposed to 10μM C_6-ceramide.

Figure 1C shows that in all cases, there is a further reduction in the recruitment of monocytes in response to ceramide after 24 hours induction of HUVEC monolayers with LPS. Monocyte recruitment in the presence of ceramide drops to about 40% of that seen in the control.

It can be seen from these figures that ceramide has a significant effect on the recruitment of monocytes to sites of inflammation, whilst having no significant effect on recruitment of monocytes to other sites.

Example 2, Effect of ceramide on the expression of adhesion molecules on the surface of U937 monocytes.

Figure 2 shows the effect of exposure of monocytes to ceramide for 16 hours on the expression of various cell surface adhesion molecules. Fig. 2 shows the effect on the expression of CD31 (Panel A), CD11a (panel B), CD26L (panel C), CD18 (panel D) and CD11B (panel E). In each case

column 1 is a negative control (no ceramide), column 2 is 20μM C_2-ceramide and column 3 is 20 μM C_6-ceramide.

Figure 2 shows that in all cases expression of the cell surface adhesion molecules is significantly reduced by addition of ceramide for 16 hours. Reduction in cell surface adhesion molecule expression results in fewer monocytes binding to the endothelial tissue at sites of inflammation.

Example 3, Effect of ceramide on the cell cycle of U937 monocytes.

Figure 3 shows the effect of ceramide on the percentage of U937 monocytes in a population entering the G0/G1 (growth arrested) phase of the cell cycle. Panel A shows the effect of C_2-ceramide on cell cycle stage after 8, 16, 20 and 24 hours exposure to media containing ceramide, and panel B shows the effect of C_6-ceramide. In all cases column 1 is a negative control, column 2 is 1 μM ceramide, column 3 is 10μM and column 4 is 20μM.

2×10^6 U937 monocyte cells were serum starved for 4 hours before the addition of media containing ceramide. The proportion of cells in the G0/G1 stage of the cell cycle was measured at 8, 16, 20 and 24 hours using flow cytometry (Nicoletti *et al*, A rapid and simple method for measuring thymocyte apoptosis by propidium iodide staining and flow cytometry,1991, J. Immunol. Methods, **139:** 271-279).

Panels A and B show an increase with time in the percentage of cells becoming growth arrested both in the presence and absence of ceramide.

The most dramatic increase in cells entering G0/G1 being seen between 8 and 16 hours, and levelling off by 20 hours. It can be seen from both panels that there is a clear trend toward cell stasis with increasing concentrations (10μM, 20μM) of both C_2- and C_6-ceramide.

This trend toward cell stasis reduces the potential for differentiation of monocytes at sites of inflammation which can contribute to joint destruction through the secretion of matrix metalloproteinases.

The data show that ceramide can reduce the recruitment of monocytes to sites of inflammation and also reduce their adhesion to these sites, it also shows that monocytes can be growth arrested by treatment with ceramide. Thus, making this naturally occurring lipid, which has no known long term side effects, a useful agent for the treatment of inflammatory disorders.

CLAIMS

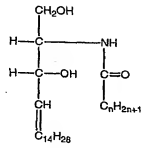
1. The use of:

(i) a ceramide, a ceramide analogue, a phytoceramide; or

(ii) a compound which is metabolisable into or otherwise capable of releasing a ceramide, a ceramide analogue or a phytoceramide; or

(iii) a compound which modulates the level of endogenous ceramide as a pharmaceutically active agent in the production of a medicament for the treatment of an inflammatory disorder.

2. The use according to claim 1, wherein said ceramide, ceramide analogue or the phytoceramide has the structure of formula 1 where n is no more than 18.



Formula 1

3. The use according to claim 2, wherein n is from 2 to 6.

4. The use according to claim 1, wherein said compound which modulates the level of endogenous ceramide is one which increases levels of endogenous ceramide or reduces the degradation of endogenous ceramide.

5. The use according to claim 4, wherein said compound is an inhibitor of alkaline or acid ceramidase.

6. The use according to any preceding claim, wherein said medicament acts by inhibiting at least one of monocyte recruitment, adhesion, transmigration to an inflammatory site and growth of proliferating monocytes.

7. The use according to any preceding claim, wherein said medicament comprises means for delivery of the pharmaceutically active agent to an inflammatory site.

8. The use according to claim 7, wherein said delivery means is a surfactant-based vesicle delivery system, a viral vector delivery system, an antibody associated delivery system or another ligand-receptor associated targeted delivery system.

9. A method of inhibiting monocyte recruitment, and/or adhesion and/or transmigration to sites of inflammation and/or of inducing growth arrest in proliferating monocytes, comprising exposing said monocytes to a therapeutically effective amount of a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolised into or breaks down to release a ceramide, a ceramide analogue, a phytoceramide in situ, or a compound which modulates the level of ceramide as a pharmaceutically active agent.

10. A method of treating a patient having an inflammatory disorder comprising, administering to said patient as a pharmaceutically active agent a therapeutically effective amount of a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolised into or breaks down to release a ceramide, a ceramide analogue, a phytoceramide in situ, or a compound which modulates the level of endogenous ceramide.

11. The method of claim 10, wherein said medicament according to the first aspect is characterised in that it acts by inhibiting at least one of and preferably all of monocyte recruitment, adhesion, transmigration to an inflammatory site and growth of proliferating monocytes.

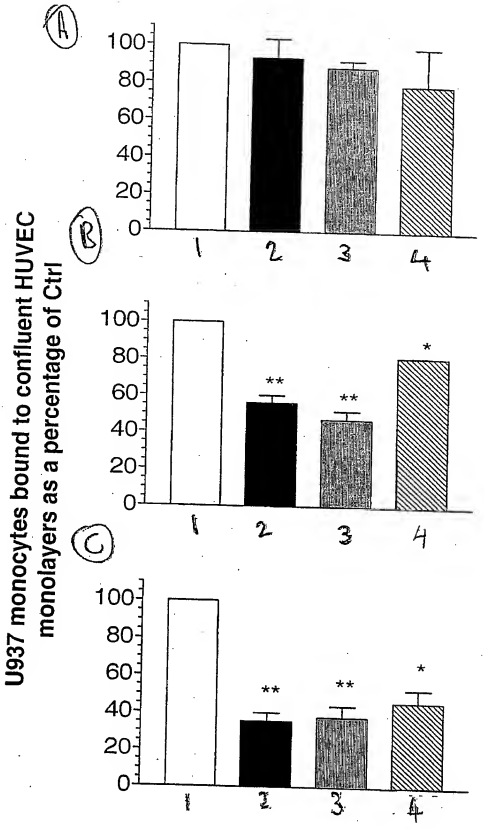
12. The method of claim 11, wherein said inflammatory disorder is rheumatoid arthritis, artherosclerosis, acute or chronic inflammatory lung disease or inflammatory bowel disease.

13. The method of any one of claims 10 to 12, wherein said pharmaceutically active agent is administered systemically, at a level to obtain a steady state blood concentration of ceramide, ceramide analogue, or phytoceramide of 1 to 20mg/l.

14. The method of any one of claims 10 to 12, wherein said pharmaceutically active agent is delivered non-systemically to achieve a concentration of ceramide, ceramide analogue, or phytoceramide in the inflammatory cells of from 100 amol to 5 fmol.

15. The method of any one of claims 12 to 14, wherein said pharmaceutically active agent is a ceramide, a ceramide analogue, a phytoceramide or a compound which is metabolisable into or otherwise capable of releasing a ceramide, a ceramide analogue or a phytoceramide, and is administered at by administering a dosage of 10 to 100 mg/day.

Fig 1



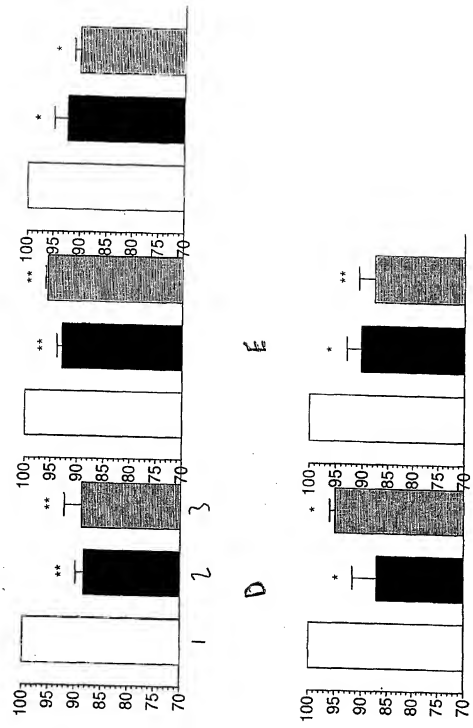
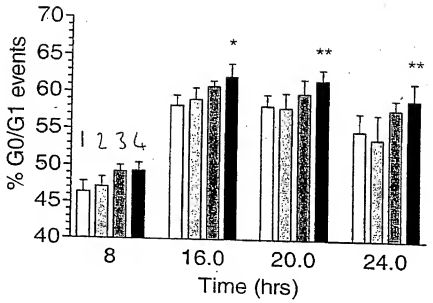

A
B
C
D
E
1
2
3
Membrane expression of adhesion molecule as a % of Ctrl.
100
95
90
85
80
75
70
*
**

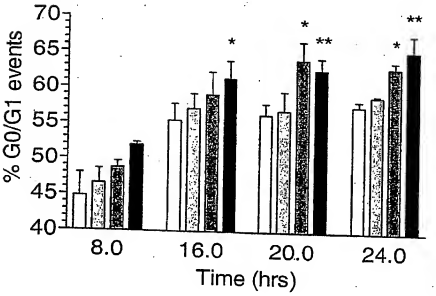
Fig 2

Fig 3

(A)



(B)



INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB2004/000173

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/164 A61P1/00 A61P9/10 A61P11/00 A61P19/02
A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/72701 A (TANG HSIN YI YVETTE ; ALI SHAUKAT (US); MAYHEW ERIC (US); JANOFF ANDRE) 4 October 2001 (2001-10-04) abstract page 1, line 1 - line 3 pages 4-7, "Summary of the Invention" page 19, line 26 - page 21, line 12 examples 1-8 table 7 claims 1-25 ----- -/--	1-3,9, 10,12-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2004	12/05/2004

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/41266 A (MERRILL ALFRED H JR ; SCHMELZ EVA M (US); BHALLA KAPIL N (US); KEANE T) 19 August 1999 (1999-08-19) abstract page 1, line 4 - line 18 page 13, line 3 - line 24 page 14, line 1 - page 17, line 21 claims 1-33	1-3,9, 10,12-15
A	WO 99/29293 A (DSM NV ; LAMBERS JOHANNES WILHELMUS JAC (NL)) 17 June 1999 (1999-06-17) abstract claims 1-13	1-3,9, 10,12-15
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 06, 22 September 2000 (2000-09-22) & JP 2000 086601 A (OTSUKA PHARMACEUTICAL CO LTD), 28 March 2000 (2000-03-28) abstract	1-3,9, 10,12-15
A	MULLIGAN M S ET AL: "ANTI-INFLAMMATORY EFFECTS OF SULFATIDES IN SELECTIN-DEPENDENT ACUTE LUNG INJURY" INTERNATIONAL IMMUNOLOGY, OXFORD UNIVERSITY PRESS, GB, vol. 7, no. 7, 1 July 1995 (1995-07-01), pages 1107-1113, XP000614962 ISSN: 0953-8178 abstract	1-3,9, 10,12-15
A	PHILLIPS, D C; ALLEN, K; GRIFFITHS, H R: "Synthetic Ceramides induce growth arrest or apoptosis by altering cellular redox status" ARCHIVES OF BIOCHEMISTRY AND BIOPYSICS, vol. 407, 2002, pages 15-24, XP002274962 abstract	1-3,9, 10,12-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 4-8,11

Present claims 1, 4-11 and 15 relate to products/methods defined by reference to a desirable characteristic or property, namely:

"a compound which is metabolisable into or otherwise capable of releasing a ceramide" (claims 1, 9, 10 and 15);
"a compound which modulates the level of endogenous ceramide as a pharmaceutically acitve agent" (claim 1);
" said compound ... is one which increases levels of endogenous ceramide or reduces the degradation of endogenous ceramide" (claim 4);
"said compound is an inhibitor of alkaline or acid ceramidase" (claim 5);
"wherein said medicament acts by inhibiting ... growth of proliferating monocytes" (claim 6);
"means for delivery of the pharmaceutically active agent to an inflammatory site" (claim 7);
"surfactant-based vesicle delivery system, ... or another ligand-receptor associated targetted delivery system" (claim 8);
"characterised in that is acts by inhibiting at least one of and preferably all of monocyte ... proliferating monocytes" (claim 11).

The claims cover all products/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the products/methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds as defined in claim 2 for the treatment of inflammatory disorders.

In addition, the expression "a ceramide analgue" is considerd to be vague and indefinite and has not been searched.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/GB2004/000173

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